NDA 13-025/S-035

JUL 26 2000

Abbott Laboratories
Attention: Jill N. Sackett
Assistant Director, Regulatory Affairs
200 Abbott Park Road, D-389 AP3O
Abbott Park, Illinois 60064-3 537

Dear Ms. Sackett:

Please refer to your supplemental new drug application dated December 4, 1996, received December 10, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tham Solution (tromethamine injection).

We acknowledge receipt of your submission dated April 2, 1999. Your submission of April 2, 1999, constituted a complete response to our August 13, 1998, action letter.

This supplemental new drug application provides for changes in the package insert labeling as required in the December 13, 1994, Federal Register Notice entitled: "*Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of 'Pediafric Use ' Subsection in the Labeling.*"

To the **PRECAUTIONS** section of the package insert, the following revisions have been made:

> **Pediatric Use:** The safety and effectiveness of THAM Solution in pediatric patients is based on over 30 years' clinical experience documented in the literature and on safety surveillance. THAM Solution has been used to treat severe cases of metabolic acidosis with concurrent respiratory acidosis because it does not raise PCO_2 as bicarbonate does in neonates and infants with respiratory failure. It has also been used in neonates and infants with hypernatremia and metabolic acidosis to avoid the additional sodium given with the bicarbonate. However, because the osmotic effects of THAM Solution are greater and large continuous doses are required, bicarbonate is preferred to THAM Solution in the treatment of acidotic neonates and infants with RDS. (Paragraph is added.)
>
> **Carcinogenesis, mutagenesis, impairment of fertility:** Studies with THAM Solution have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility. (Replaces current sentence.)

> **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when THAM Solution is administered to a nursing mother. (This section is added.)

Furthermore, we note the revisions to the **CONTRAINDICATIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION** sections of the package insert. The changes are as follows:

To the **CONTRAINDICATIONS** section of the package insert, the following sentence has been added:

> "In neonates it is also contraindicated in chronic respiratory acidosis and salicylate intoxication."

To the **ADVERSE REACTIONS** section of the package insert, the following subsection has been added:

> **Hepatic:** Infusion via low-lying umbilical venous catheters has been associated with hepatocellular necrosis.

To the **DOSAGE AND ADMINISTRATION** section of the package insert, the following subsection has been added:

> **Correction of Metabolic Acidosis Associated with RDS in Neonates and Infants:** The initial dose of Tham Solution should be based on initial pH and birthweight amounting to approximately 1 mL per kg for each pH unit below 7.4. Further doses have been given according to changes in PaO_2, pH and PCO_2.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted April 2, 1999).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 13-025/S-035." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner'[t] letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Steve McCort, Regulatory Project Manager, at (301) 827-6415.

Sincerely,

John K. Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products, HFD-5 10
Office of Drug Evaluation II
Center for Drug Evaluation and Research

THAM SOLUTION

Tromethamine Injection

For The Prevention And Correction Of Severe Metabolic Acidosis

Large Volume Glass Container

DESCRIPTION

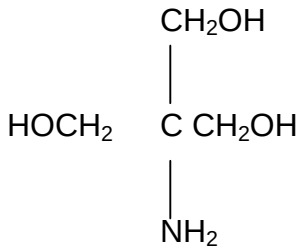
Tham Solution (Tromethamine injection) is a sterile, nonpyrogenic 0.3 M solution of tromethamine, adjusted to a pH of approximately 8.6 with glacial acetic acid. It is administered by intravenous injection, by addition to ACD blood for priming cardiac bypass equipment and by injection into the ventricular cavity during cardiac arrest.

Each 100 ml contains tromethamine 3.6 g (30 mEq) in water for injection. The solution is hypertonic (380 mOsm/liter, calc.) in relation to the extracellular fluid (280 mOsm/liter).

The solution contains no bacteriostat, antimicrobial agent or added buffer (except acetic acid for pH adjustment) and is intended only for use as a single-dose injection. When smaller doses are required the unused portion should be discarded.

Tham solution is a parenteral systemic alkalizer and fluid replenisher.

Tromethamine, USP (sometimes called "tris" or "tris buffer") is chemically designated 2-amino-2-(hydroxymethyl)-1, 3-propanediol, a solid readily soluble in water, also classified as an organic amine buffer. It has the following structural formula:



Water for Injection, USP is chemically designated H_2O.

CLINICAL PHARMACOLOGY

When administered intravenously as a 0.3 M solution, tromethamine acts as a proton acceptor and prevents or corrects acidosis by actively binding hydrogen ions (H^+). It binds not only cations of fixed or metabolic acids, but also hydrogen ions of carbonic acid, thus increasing bicarbonate anion (HCO3-). Tromethamine also acts as an osmotic diuretic, increasing urine flow, urinary pH, and excretion of fixed acids, carbon dioxide and electrolytes. A significant fraction of tromethamine (30% at pH 7.40) is not ionized and therefore is capable of reaching equilibrium in total body water. This portion may penetrate cells and may neutralize acidic ions of the intracellular fluid.

The drug is rapidly eliminated by the kidney; 75% or more appears in the urine after eight hours. Urinary excretion continues over a period of three days.

Water is an essential constituent of all body tissues and accounts for approximately 70% of total body weight. Average normal adult daily requirement ranges from two to

three liters (1.0 to 1.5 liters each for insensible water loss by perspiration and urine production). Water balance is maintained by various regulatory mechanisms.

Water distribution depends primarily on the concentration of electrolytes in the body compartments and sodium (Na+) plays a major role in maintaining physiologic equilibrium.

INDICATIONS AND USAGE

Tham Solution is indicated for the prevention and correction of metabolic acidosis. In the following conditions it may help to sustain vital functions and thus provide time for treatment of the primary disease:

1. **Metabolic acidosis associated with cardiac bypass surgery.**

   Tham Solution has been found to be primarily beneficial incorrecting metabolic acidosis which may occur during or immediately following cardiac bypass surgical procedures.

2. **Correction of acidity of ACD blood in cardiac bypass surgery**.

   It is well known that ACD blood is acidic and becomes more acidic on storage. Tromethamine effectively corrects this acidity. Tham Solution may be added directly to the blood used to prime the pump-oxygenator. When ACD blood is brought to a normal pH range the patient is spared an initial acid load. Additional tromethamine may be indicated during cardiac bypass surgery should metabolic acidosis appear.

3. **Metabolic acidosis associated with cardiac arrest**.

   Acidosis is nearly always one of the consequences of cardiac arrest and, in some instances, may even be a causative factor in arrest. It is important therefore, that the correction of acidosis should be started promptly with other resuscitative efforts. By correcting acidosis, Tham Solution has caused the arrested hear to respond to resuscitative efforts after standard methods alone had failed. In these cases, tromethamine was given intraventricularly. It is to be noted, however, that such precariously ill patients often have died subsequently of causes unrelated to the administration of tromethamine. With administration by the peripheral venous route, metabolic acidosis has been corrected in a majority of patients. The success in reinstitution of cardiac rhythm by this means probably has not been of the same order of magnitude as with the intraventricular route.

CONTRAINDICATIONS

Tham Solution is contraindicated in anuria and uremia. In neonates it is also contraindicated in chronic respiratory acidosis and salicylate intoxication

WARNINGS

1. Large doses of Tham Solution may depress ventilation, as a result of increased blood pH and reduced CO_2 concentration. Thus, dosage should be adjusted so that blood pH is not allowed to increase above normal. In situations in which respiratory acidosis may be present concomitantly with metabolic acidosis, the drug may be used with mechanical assistance to ventilation.

2. Care must be exercised to prevent perivascular infiltration since this can cause inflammation, necrosis and sloughing of tissue. Venospasm and intravenous thrombosis, which may occur during infusion, can be minimized by insuring that the injection needle is well within the largest available vein and that solutions are slowly infused. Intravenous catheters are recommended. If perivascular infiltration occurs, institute appropriate countermeasures. See ADVERSE REACTIONS.
3. Tham Solution (Tromethamine injection) should be administered slowly and in amounts sufficient only to correct the existing acidosis, and to avoid overdosage and alkalosis. Overdosage in terms of total drug and/or too rapid administration, may cause hypoglycemia of a prolonged duration (several hours). Therefore, frequent blood glucose determinations should be made during and after therapy.
4. Extreme care should be exercised in patients with renal disease or reduced urinary output because of potential hyperkalemia and the possibility of a decreased excretion of tromethamine. In such patients, the drug should be used cautiously with electrocardiographic monitoring and frequent serum potassium determinations.
5. Because clinical experience has been limited generally to short-term use, the drug should not be administered for more than a period of one day except in a life-threatening situation.

The intravenous administrations of Tham Solution can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema.

Additives may be incompatible. Consult with pharmacist, if available. When introducing additives, use aseptic technique, mix thoroughly and do not store.

PRECAUTIONS

1. Blood pH, PCO_2 bicarbonate, glucose and electrolyte determinations should be performed before, during and after administration of Tham Solution.
2. While it has not been shown that the drug increases coagulation time in humans, this possibility should be kept in mind since this has been noted experimentally in dogs.

Do not administer unless solution is clear and seal is intact. Discard unused portion.

Pediatric Use. The safety and effectiveness of THAM Solution in pediatric patients is based on over 30 years' clinical experience documented in the literature and on safety surveillance. THAM Solution has been used to treat severe cases of metabolic acidosis with concurrent respiratory acidosis because it does not raise PCO_2 as bicarbonate does in neonates and infants with respiratory failure. It has also been used in neonates and infants with hypernatremia and metabolic acidosis to avoid the additional sodium given with the bicarbonate. However, because the osmotic effects of THAM Solution are greater and large continuous doses are required, bicarbonate is preferred to THAM Solution in the treatment of acidotic neonates and infants with RDS.

Hypoglycemia may occur when this product is used in premature and even full-term neonates. See WARNINGS and ADVERSE REACTIONS.

Pregnancy Category C. Animal reproduction studies have not been conducted with tromethamine. It is also not known whether tromethamine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Tromethamine should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when THAM Solution is administered to a nursing mother.

Carcinogenesis, mutagenesis, impairment of fertility: Studies with THAM Solution have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

ADVERSE REACTIONS

Generally, side effects have been infrequent.

Respiratory: Although the incidence of ventilatory depression is low, it is important to keep in mind that such depression may occur. Respiratory depression may be more likely to occur in patients who have chronic hypoventilation or those who have been treated with drugs which depress respiration. In patients associated with respiratory acidosis, tromethamine should be administered with mechanical assistance to ventilation.

Vascular: Extreme care should be taken to avoid perivascular infiltration. Local tissue damage and subsequent sloughing may occur if extravasation occurs. Chemical phlebitis and venospasm also have been reported.

Hematologic: Transient depression of blood glucose may occur. Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection extravasation and hypervolemia.

Hepatic: Infusion via low-lying umbilical venous catheters has been associated with hepatocellular necrosis.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

OVERDOSAGE Too rapid administration and/or excessive amounts of tromethamine may cause alkalosis, hypoglycemia, overhydration or solute overload. In the event of overdosage, discontinue the infusion, evaluate the patient and institute appropriate countermeasures. See WARNINGS, PRECAUTIONS and ADVERSE REACTIONS.

The LD50 values for the acute intravenous toxicity of tromethamine are influenced by the rate of infusion of the dose administered.

Intravenous LD50 Mice - 3500 mg/kg

Intravenous LD50 Rats - 2300 mg/kg

DOSAGE AND ADMINISTRATION Tham Solution is administered by slow intravenous infusion, by addition to pump-oxygenator ACD blood or other priming fluid or by injection

into the ventricular cavity during cardiac arrest. For infusion by peripheral vein, a large needle should be used in the largest antecubital vein or an indwelling catheter placed in a large vein of an elevated limb to minimize chemical irritation of the alkaline solution during infusion. Catheters are recommended.

Dosage and rate of administration should be carefully supervised to avoid overtreatment (alkalosis). Pretreatment and subsequent determinations of blood values (e.g., pH, PCO_2, PO_2, glucose and electrolytes) and urinary output should be made as necessary to monitor dosage and progress of treatment. In general, dosage should be limited to an amount sufficient to increase blood pH to normal limits (7.35 to 7.45) and to correct acid-base derangements. The total quality to be administered during the period of illness will depend upon the severity and progression of the acidosis. The possibility of some retention of tromethamine, especially in patients with impaired renal function, should be kept in mind.

The intravenous dosage of Tham Solution may be estimated from the buffer base deficit of the extracellular fluid in mEq/liter determined by means of the Siggaard-Andersen nomogram. The following formula is intended as a general guide:

Tham Solution (mL of 0.3 M)Required =

Body Weight (kg) X

Base Deficit (mEq/liter) X 1.1*

*Factor of 1.1. accounts for an approximate reduction of 10% in buffering capacity due to the presence of sufficient acetic acid to lower pH of the 0.3 M solution to approximately 8.6.

Thus, a 70 kg patient with a buffer base deficit ("negative base excess") of 5 mEq/liter would require 70 x 5 x 1.1 = 385 ml of Tham Solution containing 13.9 g (115 mEq) of tromethamine. The need for administration of additional Tham Solution is determined by serial determinations of the existing base deficit.

Correction Of Metabolic Acidosis Associated With Cardiac Bypass Surgery: An average dose of approximately 9.0 ml/kg (324 mg/kg) has been used in clinical studies with Tham Solution. This is equivalent to a total dose of 630 ml (189 mEq) for a 70 kg patient. A total single dose of 500 ml (150 mEq) is considered adequate for most adults. Larger single doses (up to 1000 ml) may be required in unusually severe cases.

It is recommended that individual doses should not exceed 500 mg/kg (227 mg/lb) over a period of not less than one hour. Thus, for a 70 kg (154 pound) patient the dose should not exceed a maximum of 35 g per hour (1078 ml of a 0.3 M solution). Repeated determinations of pH and other clinical observations should be used as a guide to the need for repeat doses.

Correction Of Acidity Of Acd Blood In Cardiac Bypass Surgery: The pH of stored blood ranges from 6.80 to 6.22 depending upon the duration of storage. The amount of Tham Solution used to correct this acidity ranges from 0.5 to 2.5 g (15 to 77 ml of a 0.3 M solution) added to each 500 ml of ACD blood used for priming the pump-oxygenator. Clinical experience indicates that 2 g (62 ml of a 0.3 M solution) added to 500 ml of ACD blood is usually adequate.

Correction Of Metabolic Acidosis Associated With Cardiac Arrest: In the treatment of

cardiac arrest, Tham Solution should be given at the same time that other standard resuscitative measures, including manual systole, are being applied. If the chest is open, Tham Solution is injected directly into the ventricular cavity. From 2 to 6 g (62 to 185 ml of a 0.3 M solution) should be injected immediately. **Do not inject into the cardiac muscle.**

If the chest is not open, from 3.6 to 10.8 g (111 to 333 ml of a 0.3 M solution) should be injected immediately into a larger peripheral vein. Additional amounts may be required to control acidosis persisting after cardiac arrest is reversed.

Correction of Metabolic Acidosis Associated with RDS in Neonates and Infants: The initial dose of Tham Solution should be based on initial pH and birthweight amounting to approximately 1 mL per kg for each pH unit below 7.4. Further doses have been given according to changes in PaO_2, pH and PCO_2.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See CONTRAINDICATIONS.